

PENICILLIN AND SULFONAMIDES IN THE TREATMENT OF OSTEOMYELITIS AND PYOGENIC ARTHRITIS*

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THE introduction and availability, first of the sulfonamides and now of penicillin, justifies a consideration of the treatment of both acute and chronic pyogenic infections of bones and joints in the light of our present knowledge. This is because some of our previous views on this subject have been modified by the favorable results which we have observed in the use of these antibiotic agents. However, it is realized that our knowledge is still incomplete and that future observations or the introduction of new antibiotic agents may modify the methods of treatment which will be described in this paper. It is also to be noted that this discussion is limited to infections in which the pyogenic staphylococci and streptococci are the offending organisms and these comprise the great majority of the cases in both civil and military practice.

Of the various sulfonamides now available, sulfathiazole is the drug of choice in the treatment of osteomyelitis because it is more active against staphylococci than are the others and it is also effective against streptococci. Statistics indicate that in patients with osteomyelitis over two years of age staphylococci are the causative agent in over 90 per cent of the cases and in infants they are the causative agent in about 50 per cent. Almost all of the remainder are due to streptococci. Sulfadiazine and sulfamerazine have certain advantages in that they are better tolerated by some patients, but these drugs are not as effective as sulfathiazole in staphylococcic infections. Consequently, in this paper only sulfathiazole will be mentioned and it will be assumed that if this drug is not tolerated either sulfadiazine or sulfamerazine may be used.

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In comparing sulfathiazole and penicillin we find that the latter is a more potent antibacterial agent against staphylococci and streptococci, it is effective against a wider variety of organisms, and its toxicity is so low that during its administration the possibility of toxic effects need not be considered. It has the disadvantage that it is not always available, it is expensive and it is not effective when taken by mouth, but must be administered intravenously or intramuscularly or applied locally. It is excreted rapidly and if effective concentration is to be maintained in the blood it should be given by continuous intravenous drip or by intravenous injections at two-hour intervals or by intramuscular injections at three-hour intervals.

Sulfathiazole has the disadvantage that it is not as powerful an antibacterial agent as penicillin and that toxic reactions are frequent and must be watched for while the drug is being taken. These can be minimized by maintaining a large fluid intake and administering thiamine chloride. It has the advantage that it is available, is relatively cheap and is effective when taken by mouth. It can also be used locally and as the sodium salt it can be used intravenously.

Both penicillin and sulfathiazole act directly on the bacteria and the drug must come in direct contact with the bacteria in order to exert its therapeutic effect. For this reason these drugs are most effective against organisms in the blood stream or in areas of cellulitis where there is an abundant circulation in close proximity to the bacteria. In such areas the drug can diffuse into the infected tissues and reach the bacteria in sufficient concentration to exert its effect. The drugs are relatively impotent against localized infections which are surrounded by avascular scar tissue or bone or by a zone of ischemia. In lesions of this type the maintenance of an adequate concentration of the drug in the blood stream will not sterilize the focus because the drug does not enter the focus in sufficient concentration to destroy the bacteria.

It is thus evident that they are especially useful in septicemia and in spreading infections in the soft tissues and bone, but frequently fail to cure or even to favorably affect the course of chronic infections which are well walled off and isolated from the blood stream. However, when the bacteria in chronic foci become active and break through the zone which walls them off and begin to invade the surrounding tissues these drugs may stop the spread of the infection and reduce the focus to its former chronic state. Both drugs are strongly bacterio-

static and even bactericidal when applied locally and for this reason local and systemic treatment should be combined when possible. Fortunately, penicillin and the sulfonamides are not antagonistic and may be used locally or systemically in combination or one drug may supplement or supercede the other without decreasing the effectiveness of either. Finally, occasional staphylococci are resistant to either or both sulfathiazole and penicillin.

TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS

This is an acute infectious disease which is characterized by a pyogenic focus in a bone and usually this is the most important lesion. There is a variable amount of involvement of the adjacent soft tissues and the bacteria may be present in the blood and metastatic foci may develop. Until it is proved otherwise, it may be assumed that the etiological agent in every case is a staphylococcus or a streptococcus and treatment should be instituted as early as possible on this basis without waiting until the etiology is proved by culture. Fortunately, with the exception of a specific antitoxin for staphylococcic toxemia, the measures at our disposal are effective against both organisms.

The disease varies greatly in severity. It may pursue a relatively mild course and even heal spontaneously without treatment or it may be fulminating in character and the patient may even die of the generalized infection before the local lesion in the bone can be diagnosed clinically. Fortunately, these cases of fulminating septicemia from an obscure focus in a bone are very rare. In the average case the patient is quite sick with high fever, mild septicemia and a definite and recognizable lesion in the involved bone. In the past the mortality was about 25 per cent and a large percentage of the survivors were afflicted with chronic osteomyelitis and the crippling which may result from this disease. By physiological treatment combined with local rest and carefully applied surgery we were able not only to reduce the mortality to about 10 per cent, but to lessen the incidence and severity of the sequelae of the acute disease.

With the advent of the sulfonamides we had, for the first time, an agent which, when administered systemically, was effective against the causative organisms. The more recent discovery and availability of penicillin places in our hands a safer and more powerful antibacterial agent. It is thus evident that our treatment must be revised. Even

before the discovery of the sulfonamides there was a definite trend towards less precipitate and radical surgery and more physiological care of the patient.

Some observers considered acute osteomyelitis a systemic infection of which the local lesion in the bone was only an unimportant part and advised against surgery. I considered the focus in the bone the cause of the toxemia and septicemia and thought that this focus should be drained as early in the disease as the operation could be performed with safety; that is, as soon as the condition could be diagnosed and the patient could be gotten in suitable condition for the operation (Key^{1, 2, 3, 4}). It is not surprising that some observers now advocate chemotherapy alone and not only think that surgery is harmful (Baker, Schaubel and Kuhn⁵), but have also discontinued immobilization of the extremity (Hoyt, Davis and Van Buren⁶).

The objectives of treatment are to save the life of the patient, prevent spread of the local disease, clear the blood stream of bacteria, sterilize the focus in the bone, promote healing of the infected and damaged tissues and maintain or restore the health of the patient.

Since the effectiveness of penicillin and the sulfonamides varies directly with the ability of the blood stream to carry the drug to the bacteria, it is important that the treatment with these drugs be instituted as early in the disease as possible, even before the diagnosis can be made if the patient is seen that early. This is in order that the drug may reach the bacteria before extensive necrosis of bone and soft tissue occurs and they become separated from the blood stream by a wide and relatively impermeable zone of necrotic and inflammatory tissue. In a child with fever, localized tenderness, pain and loss of function in one extremity, acute hematogenous osteomyelitis or pyogenic arthritis should be suspected and the patient should be given a full dose of sulfathiazole immediately and hospitalized as soon as possible. The sulfathiazole should be continued until the symptoms subside or treatment with penicillin can be instituted or a diagnosis of some condition which is not amenable to this treatment is made. Localized joint or bone tenderness, muscle spasm, swelling, heat, redness and fluctuation confirm the diagnosis, but treatment should be instituted before these signs appear. This is not scientific medicine and will cause the drug to be administered to a few patients in whom it is not indicated. but I believe that it will do little harm and may abort many

cases of osteomyelitis.

Unfortunately, in the great majority of instances the nature of the disease is not suspected until the lesion in the bone is well advanced. When the patient is first seen by the surgeon or enters the hospital he has a high fever, is toxic and dehydrated and exhausted by pain and lack of sleep.

When this patient enters the hospital he should be given a sedative if necessary and subjected to a careful, but gentle physical examination in order to determine the nature, location and severity of his disease. Fluids should be given by mouth and physiological salt solution which contains 5 per cent glucose should be administered intravenously until the dehydration has been corrected. Blood should be taken for culture and for matching for transfusion. A white blood cell count, differential count, red blood cell count and estimation of the hemoglobin should be done and the urine examined.

If penicillin is immediately available a full dose (5,000 to 20,000 units) should be given intravenously or intramuscularly as soon after admission as possible and the intramuscular administration of from 2,000 to 15,000 units should be repeated every three hours until improvement is noted. Then the dose may be decreased. In some clinics the penicillin in amounts of from 60,000 to 100,000 units in 24 hours is given by continuous intravenous drip to very sick patients.

If penicillin is not immediately available, a full dose of sodium sulfathiazole should be given intravenously if the patient is very ill (5 to 30 grains) or sulfathiazole by mouth and its administration by mouth or intravenously if necessary in full doses every three hours should be continued until improvement or toxic manifestations justify a reduction in the dosage or until penicillin is substituted. While the patient is taking sulfonamides the urine should be examined daily and the urinary output maintained.

If facilities are available for determination of the level of the drug in the blood, this should be done and the dosage of sulfathiazole and fluid intake so balanced that a level of from 4 to 6 mgm. per cent is maintained. But the fluid intake should not be restricted in order to raise the level of the drug in the blood. This may lead to increased toxicity from the infection and from the drug. Robertson⁷ gave from 4 to 9 grams of sulfathiazole daily to children and it is to be noted that children are more tolerant of the drug than are adults.

The affected limb should be immobilized in a large hot wet dressing with a splint or traction if necessary. This dressing should not be changed, except for examination of the part. Its principal functions are to relieve pain and immobilize the extremity. Frequent change of the hot wet dressing defeats both of these objectives. If it is covered with waterproof material the body heat of the patient will keep the dressing warm or hot water bags may be applied around it.

If the patient is anemic a small transfusion of from 100 to 250 cc. of blood should be given and this should be repeated daily until the anemia is corrected. He should be given large amounts of vitamin B and C as long as the disease is active.

In some clinics (Baker⁵) staphylococcus antitoxin is given to combat the toxemia when this is indicated by a marked shift to the left in the differential count of the white blood cells. I have had little experience with this antitoxin, but believe that if properly used it is a valuable agent in the treatment of very ill patients who are toxic from staphylococcic infection. It must not be relied upon to cure the disease because it has no effect upon the bacteria, but merely tends to neutralize the toxins which they produce.

Of the above therapeutic measures, sedation, sulfathiazole or penicillin, immobilization of the part, intravenous fluids and transfusion, if necessary, should be instituted as soon as possible after admission to the hospital and the patient should then be left alone and permitted to rest.

It is noted that the x-ray is not mentioned. This is of no value in the early diagnosis of the disease and the patient should not be subjected to an x-ray examination until a week or more after the onset when sufficient time has elapsed for changes to occur in the bone which will be visible in the roentgenogram.

The question now arises as to whether or not surgery is indicated. In the past I have maintained that the focus in the bone should be drained as soon as the patient is ready for the operation; that is, after the above measures have been instituted and the dehydration has been corrected and he has rested and his general condition has improved to a point where the operation can be performed with relatively little risk. I now think that it is time to reconsider that opinion, because the principal reason for the operation was to relieve the tension in the bone and prevent or lessen the spread of the infection. We now have

sulfathiazole and penicillin which tend to limit the spread of the infection and gradually to lessen the tension in the bone. If treatment is started early it seems probable that these agents can sterilize the focus in the bone and so limit the necrosis of bone that gross sequestra will not form.

On the other hand, if the specific treatment is started relatively late in the disease (4 to 7 days after the onset) it is probable that the focus in the bone is so well established and so extensive that the drug cannot enter the abscess in sufficient concentration to kill the bacteria. Under these conditions it is still my opinion that the focus in the bone should be drained as soon as the patient is ready for the operation and the focus can be identified and approached surgically. In infants (under two years of age) the bones are so porous that operation on the bone is not necessary and the abscess in the soft tissue may be aspirated or drained by a small incision and usually the dead bone will be absorbed and replaced without sequestration. But in older children it is probable that intense chemotherapy or penicillin may cause the acute disease to subside and leave a chronic infected focus in the bone which may flare up when activity is resumed or at some later date. I have seen both of the above sequences of events occur in patients who had been treated elsewhere.

The operation may be done under general or local anesthesia and is a relatively simple and non-shocking procedure. The bone is exposed through the shortest and safest route and the periosteum split and two or more small drill holes are made through the cortex. A small window may then be removed from the cortex but no attempt is made to remove the infected cancellous bone or marrow. Hemostasis is effected, the wound is sprinkled with sulfathiazole powder and packed loosely with vaseline gauze and the extremity is immobilized in a well-padded plaster-of-Paris cast. If penicillin is available the vaseline gauze is put only around the margins and walls of the wound and a small catheter is placed in the depth of the wound and led out through the dressing and the cast and a small amount of penicillin (5 to 10 cc. of a solution containing 250 units per cc.) is instilled into the wound once or twice daily.

Immobilization is a very important part of the treatment and should be continued until the wound is almost healed or until chronic osteomyelitis is present and there is sufficient involucrum to prevent a patho-

logical fracture. The general supportive treatment should be continued as indicated until the improvement in the patient's general condition warrants a return to a normal regime.

It is to be emphasized that the operation is for drainage only and is a relatively mild procedure. When properly performed and rightly timed and followed by effective immobilization of the part, I do not believe that the drainage operation does any harm. I have seen patients in whom the disease appeared to spread widely through the bone and cause extreme destruction and involvement of the adjacent joints and even develop secondary foci while being treated with sulfathiazole. It is reasonable to think that early drainage of the focus in the bone would have lessened the spread of the disease in these patients.

When should the operation be performed? I see no reason for waiting until the temperature is normal and the acute infection has subsided. If the patient's general condition warrants the administration of a local or short general anesthetic (inhalation or pentothal) and the focus can be identified with a fair degree of certainty the focus should be drained. This operation is not performed as an emergency, but is done when the condition of the patient is satisfactory and at the convenience of the surgeon and the staff. In some patients it may be done on the day after admission or even on that day and others may enter the hospital with a severe septicemia and profound toxemia and may die of the infection or recover and the local disease subside without being fit subjects for a drainage operation at any time. If the disease is limited to cancellous bone sequestration may not occur, even in older children with severe infection.

It is possible that further experience with penicillin will cause this opinion to be revised, but I doubt it. When the disease is well advanced dead bone is present and, especially in older children, this will sequestrate and be difficult to sterilize by systemic treatment. The fact that the local and general symptoms have subsided does not mean that the patient is cured of osteomyelitis.

In pyogenic joints the situation is different and a sulfathiazole suspension or, better, penicillin can be injected directly into the joint cavity in sufficient amounts (10,000 to 40,000 units) to kill all susceptible bacteria in the joint and in the synovial tissues. If this is combined with adequate systemic treatment and is done before the cartilage is destroyed, the joint may be saved and a prompt restoration of func-

tion may be expected. The injection is made in sufficient normal salt solution to distend the joint cavity slightly and is repeated daily until the general and local symptoms subside. If the patient is seen late, after the cartilage is destroyed, the joint should be drained and then immobilized in a functional position and local and systemic administration of the drug continued just as was described for the infection in the bone.

Infected compound fractures should be treated roughly as described above, except that adequate drainage followed by reduction and immobilization are important parts of the treatment and the operation should be done as soon as the patient can be gotten in satisfactory condition. If gas bacillus infection is present the appropriate antitoxin may be combined with the penicillin or sulfathiazole and the operation should be performed as soon as possible and the involved muscles excised widely or the extremity amputated if it is devitalized.

THE TREATMENT OF CHRONIC OSTEOMYELITIS

In this condition surgery is usually necessary if the disease is to be cured, but sulfathiazole and penicillin are useful adjuncts to our surgery and are also useful in quieting down acute flare-ups of the chronic infection.

In a chronic osteomyelitis the disease may remain quiescent without drainage or other symptoms over a variable period and the focus may then become painful and acutely inflamed and an abscess may develop and rupture spontaneously unless it is drained. Or a sinus may close spontaneously and then pain, local inflammation and an abscess may develop. As a rule, these acute exacerbations of the disease are not accompanied by much fever, nor is the patient dangerously ill. However, this is not always true and they should not be taken too lightly, because sometimes the disease becomes invasive in character and may cause septicemia and even death.

In the past we have treated these acute exacerbations of the disease by rest in bed, forcing fluids and hot, wet packs and immobilization of the extremity and surgical drainage. Now, with sulfathiazole or penicillin added to the above measures, we frequently see the acute symptoms subside without abscess formation and the patient may again resume work within a relatively short time or he may elect to submit to an attempt to cure the disease by a radical surgical procedure. If abscesses form they should be drained as in the past.

In considering the surgical treatment of chronic osteomyelitis, the operation for cure should be undertaken only while the disease is relatively quiescent; that is, when fever, pain and local signs of acute inflammation are absent. Then, the patient should be hospitalized a day or two before the operation and penicillin or sulfathiazole administered in moderate doses (10,000 units of penicillin intramuscularly every 3 hours or 15 grains of sulfathiazole by mouth every 4 to 6 hours).

The operation should be performed just as carefully and thoroughly as though the drug were not being used and an attempt should be made to remove all sequestra and as much as possible of the dead and infected bone and to saucerize the cavities in the bone and eliminate the dead space. The infected walls of the sinuses are also excised. The wound is then sprinkled with sulfathiazole and sutured and the extremity is immobilized in a plaster-of-Paris cast. Dry penicillin powder may be mixed with the sulfathiazole powder or a small catheter may be placed in the bottom of the wound and the wound sutured around it and penicillin instilled into the wound daily for a week or so after the operation. The systemic administration of the drug is continued for from one to two weeks after the operation, or until the wound is healing. Depending upon the lesion, the cast is removed in from two to four weeks after the operation. Healing and probable cure can be obtained in about 60 per cent of the cases.

In those cases in which the operation fails in that the wound does not heal by primary intention after it is sutured, I have not found that the attempt to close it has precipitated a severe infection, but has resulted in a reduction of the size of the open wound and is followed by one or more sinuses which lead to infected bone. In other instances the wound will be healed when the cast is removed, but it will exhibit signs of infection or sinuses may develop when function is resumed, or at some later date. In these it will be found that the operation has been inadequate. The principal reasons for failure in my hands have been incomplete removal of sequestra, insufficient removal of dead or infected bone, inability to obliterate dead spaces, closure with too much tension and inability to close the wound because of damage to the soft tissues by previous surgery and long continued infection.

The use of adequate surgery within a few months after the subsidence of the acute disease would eliminate a considerable proportion of the severe cases of chronic osteomyelitis with large eburnated bone

containing one or more large cavities and a variable number of small foci of disease. Such cases may be incurable by anything short of amputation and neither sulfathiazole nor penicillin can be expected to solve the problems which they present (Key⁸).

The dead bone should be removed as soon after the subsidence of the acute infection as it can be identified. It is wrong to wait for it to sequestrate or for a massive involucrum to form. The dead bone harbors infection and the massive involucrum becomes chronically infected as it is formed. Even if a pathological fracture is produced or follows the operation, this will do no great harm if the extremity is properly immobilized after the operation. Likewise, even if it is not possible to identify and remove all of the dead bone at the first operation something will be gained and a second or third operation may be performed if necessary. There is no reason why a surgeon should not plan to cure a chronic osteomyelitis by a series of operations, just as a plastic surgeon plans to replace extensive scar tissue by a series of skin grafts. The same is true of infected compound fractures. The surgeon should not wait for many months or years until the infection is almost incurable before attempting to create conditions favorable for elimination of the infection. The re-inforcement of good surgery by sulfathiazole or penicillin justifies a more aggressive attitude on the part of the surgeon in his war on infection in bone. On the other hand, he should do as little harm as possible and avoid the removal of living bone which may aid rather than interfere with healing. It is thus evident that subperiosteal resection is not recommended. Rather, one should perform a meticulous removal of as much dead and infected bone as possible.

From what has been written above it may be inferred that I no longer use or recommend the Orr treatment for chronic osteomyelitis. This is not the case. I both use and recommend it. It is used in wounds which cannot be closed satisfactorily and in wounds in which the infection for some reason seems too virulent to permit primary closure. This is especially true of extensive infections with large sequestra and foul-smelling, brown colored saprophytic pus. These foci are treated as adequately as possible, then sprinkled with sulfathiazole, packed loosely with vaseline gauze and immobilized in a plaster cast, or penicillin may be instilled through a catheter led out through the cast. They usually require one or more operations after the severe infection has subsided and may be closed or not, depending upon the state of

the wound at the end of the operation. The drug is also administered systemically both before and for a week or so after operation.

CONCLUSION

Acute and chronic osteomyelitis are surgical conditions in which sulfathiazole and penicillin are valuable adjuncts to, but rarely substitutes for sound surgical treatment.

REFERENCES

1. Key, J. A. Prevention of chronic osteomyelitis; early diagnosis and treatment of acute osteomyelitis, *J. Missouri M. A.*, 1936, 33:39.
2. Key, J. A. Rational treatment of acute hematogenous osteomyelitis, *J.A.M.A.*, 1938, 111:2163.
3. Key, J. A. Early operative treatment of acute hematogenous osteomyelitis, *Surgery*, 1941, 9:657.
4. Key, J. A. Sulfonamides in the treatment of chronic osteomyelitis, *J. Bone & Joint Surg.*, 1944, 36:63.
5. Baker, L. D., Schaubel, H. J. and Kuhn, H. H. Open versus closed treatment of acute osteomyelitis; a clinical report on the use of antitoxin and the sulfonamide drugs with and without early drainage, *J. Bone & Joint Surg.*, 1944, 26:345.
6. Hoyt, W. A., Davis, A. E. and Van Buren, G. Acute hematogenous staphylococcal osteomyelitis; treatment with sulfathiazole without operation, *J. A. M. A.*, 1941, 117: 2043.
7. Robertson, D. E. Medical treatment of hematogenous osteomyelitis, *Ann. Surg.*, 1943, 118: 318.
8. Key, J. A. Amputation for chronic osteomyelitis, *J. Bone & Joint Surg.*, 1944, 26: 350.